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# Are we really what we eat? Nutrition and its role in the onset of rheumatoid arthritis

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**Abstract**

Accumulating research evidence suggests that individual dietary factors and dietary patterns might be implicated in the risk of development of rheumatoid arthritis (RA). This narrative review aims to present this evidence and provide nutritional recommendations for reducing RA risk in susceptible individuals. Overall, a 'Western' type diet rich in energy intake, total and saturated fat, an unbalanced ratio of n-3 to n-6 fatty acids, high in refined carbohydrates and sugar and low in fiber and antioxidants might increase the risk of RA both directly through increasing inflammation and indirectly through increasing insulin resistance and obesity, with the latter being a known risk factor for RA. On the contrary, consumption of long-chain omega-3 polyunsaturated fatty acids, derived from fish and fish oil, is associated with a reduced risk of RA probably due to their anti-inflammatory properties. The Mediterranean diet (MD), rich in plant-based foods such as wholegrains, legumes, fruit, vegetables, extra-virgin olive oil and low in red meat consumption, might have the potential to reduce the risk of RA. Based on current research evidence, it is suggested that adherence to the MD enhanced with an increased consumption of fatty fish, reduced consumption of sugar-sweetened drinks and maintenance of a normal body weight, contributes to reducing the risk of RA. Further research on RA susceptibility will allow for more specific dietary recommendations to be made.

**Key words**: rheumatoid arthritis, Western diet, Mediterranean diet, nutrients, obesity, metabolic syndrome, inflammation

**Abbreviations**

Alternative Healthy Eating Index (AEHI-2010), anti-cyclic citrullinated antibody (ACPA), body mass index (BMI), cardiovascular disease (CVD), C-reactive protein (CRP), docosahexanoic acid (DHA), eicosapentanoic acid (EPA), food frequency questionnaire (FFQ), glycaemic index (GI), healthy controls (HC), inflammatory polyarthritis (IP), interleukin-6 (IL-6), long-chain n-3 polyunsaturated fatty acids (LC-PUFAs), Mediterranean diet (MD), metabolic syndrome (MetS), Nurses' Health Study

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(NHS), rheumatoid arthritis (RA), tumor necrosis factor- α (TNF-α), white adipose tissue (WAT)

**Highlights**

- Dietary factors might be environmental triggers in rheumatoid arthritis (RA).
- Increased meat, salt and excessive free fructose consumption potentiate RA risk.
- Obesity shares common inflammatory links with RA and should be addressed in pre-RA.
- The Mediterranean diet and fatty fish might reduce risk of RA development.

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## 1. Introduction

Rheumatoid arthritis (RA) is a long-term, autoimmune inflammatory condition affecting around 0.25% of the global population [1]. The exact aetiopathological factors for disease development are not yet fully understood, although it is known that susceptibility to RA is determined by several genetic and environmental factors. The latter includes for example the well-established link between a major environmental agent, tobacco smoking and disease onset [2]. In recent years, an increasing number of studies have attempted to explore the role and impact of nutrition in both RA prevention, as well as in disease management. Whereas, however, studies have reported on various nutrients, antioxidants, vitamins and other factors implicated in the risk of RA development, many have failed to show statistical significance and reproducibility leaving the evidence weak and controversial in some aspects. In this narrative review, we aim to explore and highlight some of the evidence that has been linked to the risk of developing RA.

## 2. Diet and RA risk

### *2.1 Dietary factors as 'triggers' of disease*

Evidence suggests that dietary factors might act as environmental triggers in genetically susceptible individuals leading to the development of RA with a role in enhancing the systemic immune-inflammatory response. The inflammatory process in RA involves a cascade of 'events', including production of soluble immune mediators such as cytokines and chemokines by joint tissue cells such as synovial fibroblasts, synovial macrophages and chondrocytes ultimately resulting in joint damage [3]. A cascade of inflammatory reactions with production of acute phase proteins, including C-reactive protein follow enhancing the inflammatory nature of the disease [3]. Diet as an environmental factor may act both as a disease trigger or a 'moderator' through foods that either exacerbate (e.g. red meat, salt, excessive food intake) or reduce inflammation (e.g. fatty fish, fruit and vegetables) [4-6]. Indeed, the trend towards a higher prevalence of autoimmune diseases, including RA, in Western societies as opposed to the Eastern world and developing countries [7], implicates a number of possible environmental triggers. These include the 'hygiene hypothesis', stating that high standards of hygiene can limit

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exposure to pathogens that are potentially beneficial to the immune function thereby increasing susceptibility to autoimmune conditions [8], psychosocial stress, smoking, increased alcohol consumption, dietary habits and obesity [9]. In particular, a 'Western' diet, characterized by increased consumption of saturated and trans fats, low ratio of omega-3:omega 6 fatty acids and an excessive consumption of refined carbohydrates and sugar-sweetened drinks, increases the risk of RA both directly through increasing inflammation [6;10] and indirectly through increasing insulin resistance, obesity and associated co-morbidities [11].

Central to the Western dietary pattern, a high consumption of red meat, meat and meat products, and total protein were associated in a nested case-control study with an increased risk of inflammatory polyarthritis (IP) [12]. In particular, in multivariate adjusted models, intake of more than 88 g red meat/day, compared to less than 49 g/day, doubled the risk of developing IP (odds ratio: 2.3, 95% CI: 1.1-4.9; p=0.03) [12]. These findings however were not confirmed in the Nurses' Health Study (NHS) of 82 000 women whereby diet data collection was performed using a semi-quantitative food frequency questionnaire (FFQ) provided 6 times over a 22-year period [13]. A recently published multi-centered case-control study conducted in China, including 968 RA patients and 1037 healthy controls (HC) assessing dietary intake 5 years before disease onset, showed that RA patients consumed more potatoes and less chicken, fish, mushrooms, beans, dairy products, citrus fruits and organ meats compared to HC, but found no significant differences in red meat consumption between the two groups [14]. Discrepancies between studies may reflect methodological differences regarding diet data collection (method used and time point of collection) and populations studied (ethnicity, sex, education and socioeconomic factors). The overall diet consumed by the study's population (amount and food types) is also of interest since nutrients may act synergistically in reducing inflammation and oxidation (such as in the case of vegetables and olive oil as discussed in Section 2.3), as well as have an 'additive' effect (such as in the case of increased consumption of meat and saturated/trans fatty acids) in aggrevating inflammation.

Despite the controversy of published study data, there appear to be a number of possible mechanisms linking a high red meat consumption to RA risk such as meat fat

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and nitrites which increase inflammation [15], increased iron intake which aggravates inflammation in rheumatoid synovial membranes [16], possible changes in gut microbiota [17] as well as the possibility of meat 'displacing' consumption of protective foods such as fish. Additionally, an increased sodium (salt) intake, also characteristic of the 'Western' diet, has been associated with a higher risk of RA with a dose-response relationship between sodium intake and diagnosis of RA [18]. Pathways of inflammation caused by sodium chloride have been recently reviewed [5] bringing back to light the potential deleterious effects of high sodium chloride consumption. In line with this, an increased risk of anti-cyclic citrullinated antibody (ACPA) positivity [19], (suggesting a high risk of imminent RA in those without disease) has been reported among high sodium intake (heavy) smokers [20] . Yet, mechanisms for the latter remain unclear and despite the suggestion that high salt consumption impacts on immune reactions in RA pathways, evidence suggests that this effect may be seen only in the presence of other environmental factors such as smoking [20]. Larger studies are thus needed to reach more concrete conclusions.

***2.2 Co-morbidities related to diet as disease 'triggers'***

Co-morbidities in RA, aside from being increasingly prevalent at disease onset [21], add to the burden of disease over time and prevent the achievement of good treatment outcomes [22]. A good and recent example for the latter is the impact of a high body mass index (BMI) on treat-to-target goals in RA, emphasizing the importance of targeting obesity as part of the routine management of RA [23].

Obesity, defined as excessive fat accumulation is promoted by overconsumption of energy-dense diets and leads to the accumulation of white adipose tissue (WAT) and systemic inflammation. WAT, is not inert, but instead acts as an "endocrine organ" releasing pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), leptin, resistin, and C-reactive protein (CRP) [24]. Visceral obesity, in particular, and the metabolic syndrome (MetS), characterized by a constellation of conditions including insulin resistance, hypertension and dylipidaemia, predispose individuals to autoimmune inflammatory disease through increasing inflammation and associated co-morbidities [11]. Indeed, obesity represents an important and rising

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comorbidity even on first presentation of RA [21] and is a key determinant of insulin resistance, even more so than circulating proinflammatory cytokines [25].

The MetS, is also associated with a high risk of RA [26] and the finding that it is already present in early-diagnosed RA [27] underscores its role as a risk factor and further highlights the importance of diet and optimal glycaemic and lipid control among other. Furthermore, chronic inflammation in patients with RA also accelerates atherosclerosis, with the risk of cardiovascular mortality in patients with RA being 50% higher than in the general population [28]. RA is indeed significantly associated with subclinical atherosclerosis and cardiovascular disease risk [29]; a risk that may be exacerbated by the chronic use of pharmacological therapy. Indeed, (inappropriate) use of glucocorticoids in the treatment of arthralgia or other pre-clinical states of RA can exacerbate weight gain, insulin resistance and increase the risk of diabetes thus increasing the risk of CVD even further.

### *2.3 Dietary factors for disease prevention*

Evidence suggests that consumption of individual foods might reduce risk of RA; a good example of this being fish. In particular, dietary long-chain n-3 polyunsaturated fatty acids (LC-PUFAs, the main source being fish) of more than 0.21 g/day was associated with a 35% decreased risk of developing RA compared with a lower intake in women [30]. Additionally, a large Danish prospective population-based cohort study demonstrated that an increase in intake of 30 g fatty fish (≥ 8g fat/100 g fish) per day was associated with a 49% reduction in the risk of RA while the intake of medium fat fish (3-7 g fat/100 g fish) was associated with a significantly higher risk [31]. The EIRA study, a population-based case-control study of more than 4000 participants, however, did not confirm these findings since it was shown that regular consumption of fatty fish was associated with only a modestly decreased risk of developing RA [32], perhaps due to the broad categorization of fish intake as 1–7 times/week, 1–3 times/month, seldom or never.

The risk reduction associated with a higher intake of omega-3 fatty acid intake is not surprising due to their strong anti-inflammatory properties. LC-PUFAs and in particular, eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), are capable of partly inhibiting inflammation including leucocyte chemotaxis, adhesion molecule

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expression and leucocyte–endothelial adhesive interactions, production of eicosanoids such as prostaglandins and leukotrienes from the n-6 fatty acid arachidonic acid and production of pro-inflammatory cytokines [33]. In addition, EPA and DHA give rise to the anti-inflammatory and inflammation resolving mediators, resolvins, protectins and maresins. Mechanisms underlying the anti-inflammatory actions of EPA and DHA include altered cell membrane phospholipid fatty acid composition, disruption of lipid rafts, inhibition of activation of the pro-inflammatory transcription factor nuclear factor κB so reducing expression of inflammatory genes and activation of the anti-inflammatory transcription factor peroxisome proliferator-activated receptor γ [33]. In fact, very strong correlations have been found between n-3 LC-PUFA intake and synovial fluid n-3 LC-PUFA in rheumatoid patients, while n-3 LC-PUFA in plasma and synovial fluid correlated inversely with pain score [34].

In some studies, intake of fruit and vegetables has been associated with increased risk of RD. In the EPIC-Norfolk study [35], patients with IP were found to consume less fruit and vitamin C than matched controls, whereas a case-control study showed that cooked vegetables and olive oil were inversely and independently associated with the risk of developing RA [36]. Possible mechanisms include the antioxidant properties of fruit and vegetables as well as natural tocopherols in olive oil acting as radical scavengers [37]. On the other hand, the large Danish prospective study discussed earlier, failed to find any associations between RA and the intake of citrus fruit, vegetables, retinol, beta carotene, vitamins A, E, C and D, zinc, selenium, iron and meat [31]. The reasons for the null findings are not clear but may relate to the types and amounts of fruit and vegetables consumed and the overall dietary pattern.

Potential associations between sugary drinks and RA development have also been described. For example, in the NHS, it has been shown that regular consumption of sugar-sweetened soda, but not diet soda, is associated with an increased risk of seropositive RA [38], while consumption of high-fructose corn-syrup sweetened soft drinks, fruit drinks and apple juice 5 or more/week has been associated with arthritis in young US adults [39]. In relation to this, it is hypothesized that consumption of excess free fructose (defined as fructose to glucose ratio >1:1) contributes to fructose reactivity in the gastrointestinal tract and intestinal in situ formation of advanced glycation end

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products, which once absorbed, travel beyond the intestinal boundaries to other tissues and promote inflammation [39].

Further evidence and in particular a meta-analysis of coffee and tea consumption on the risk of RA, suggests that consumption of 4 or more cups coffee/day increases risk of seropositive, but not seronegative RA [40]. However, the results should be interpreted with caution due to the possibility of other potential confounders such as cigarette smoking, stress and lower dietary quality in those consuming an excessive amount of coffee. The same meta-analysis found no association between tea consumption and risk of RA [40]. In terms of alcohol, consumption of 3-5 standard drinks/week has been associated with 22-31% reduced risk of developing RA compared to no alcoholic drinks [41].

### 2.4 Healthy Dietary Patterns: The Healthy Eating Index and the Mediterranean Diet

The consumption of specific types of diets as opposed to individual foods has led to a number of studies exploring the impact of different diets/dietary patterns on disease expression and outcomes.

An important example includes a prospective follow-up of NHS I and NHS II, assessing long-term dietary quality and risk of RA using the 2010 Alternative Healthy Eating Index (AEHI-2010) based on Dietary Guidelines for Americans [42]. It was shown that the risk for incident RA according to cumulative AEHI-2010 guidelines were 29% and 35% lower for all RA and seropositive RA respectively [42]. On the contrary, co-analysis of data from the same cohorts assessing the adherence to the MD with RA risk found no associations [43] while findings were also nil in a case-control study of MD adherence and RA risk [44].

The MD is characterized by an abundance of plant foods such as unrefined cereals, fruit, vegetables, legumes and extra-virgin olive oil olive oil, a moderate consumption of poultry, dairy products and eggs and a low consumption of sweets and red meat. Alcohol, especially red wine, may also be consumed with meals while herbs and spices are central to the health-promoting characteristics and food palatability of this dietary pattern [45;46]. A recently published systematic review on MD and RA

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concluded that 'there is currently insufficient evidence to support widespread recommendation of the MD for prevention of RA' but it 'may provide a secondary benefit, of lessening future complications of the disease' [47]. Indeed, an umbrella review of meta-analyses of observational studies and randomized trials including more than 12 800 000 subjects found that greater adherence to the MD was supported by robust evidence to reduce the risk of overall mortality, cardiovascular disease, overall cancer incidence, neurodegenerative disease and diabetes, while suggestive evidence was also found supporting the greater effectiveness of the MD in reducing weight, BMI and waist circumference, lowering total cholesterol concentration and increasing HDL-cholesterol concentration, when compared to control diet [48].

The MD's protective properties are thought to be through antioxidant and anti-inflammatory mechanisms [4] stemming from a combination of the high intake of monounsaturated fatty acids (MUFA) and polyphenols from olive oil, comprising about 85% of the fat content of the MD, which is indeed a high fat diet, LC-PUFA from fish, and antioxidants from extra-virgin olive oil, fruit, vegetables and wine [45;49]. Olive oil not only provides polyphenols and tocopherols but also facilitates the intake of vegetables, legumes and cereals containing low glycaemic index (GI) carbohydrates with important health promoting properties such as reduction in insulin resistance, diabetes and CVD [37;50].

**3. Dietary recommendations for RA risk reduction**

Based on the evidence reviewed it is evident that healthy dietary habits are important for reducing the risk of RA and associated co-morbidities. In this respect, we advocate adhering to the MD pattern, with an increased consumption of 'fatty' fish, these being sardines, salmon, seabeam, seabass and trout, to enhance its anti-inflammatory properties. The MD is a plant-based diet abundant in wholegrains, legumes, 5 or more fruit and vegetables per day, preferably seasonal and produced locally, daily consumption of extra-virgin olive oil along with 1-2/week consumption of fatty fish, weekly consumption of other types of fish and poultry, and limited consumption of red meat to 1-2 per month. We advocate avoiding or at least reducing consumption of sugar-sweetened drinks, limiting coffee consumption to 3 cups a day, and if alcohol is consumed, drink in

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moderation and with meals. It is imperative to balance intake with requirements by controlling portion sizes, reducing consumption of high-fat and sugar foods and drinks, and engaging in daily physical activity aiming to achieve and maintain a normal body weight [51]. Patients on glucocorticoid treatment and at risk of endocrine/metabolic morbidities, further benefit from reduction in sugar and salt intake and low GI foods which result in a slow and sustainable release of blood glucose and reduce insulin resistance [50]. Calcium and Vitamin D supplementation, where indicated, for optimal bone health as well as weight-bearing exercises, are also important dietary and lifestyle habits that should be considered. Patients at risk of RA or with potential pre-RA manifestations such as arthralgia should be referred to registered dietitians for individualized dietary advice.

**4. Conclusion**

In conclusion, although evidence on specific nutrients and dietary patterns has been subject to much controversy and discussion over the years, there is no doubt that healthy eating and drinking does really determine what we are and what becomes of us, at least in some respects. Incorporating dietary and lifestyle advice in the pre-clinical phase of disease and in patients with arthralgia (with no RA disease manifestations) could determine at least in part, what happens next. We trust that the rising recognition of the impact of nutrition in RA in the pre and post clinical stages will encourage dietary advice by registered dietitians, to become central to the management of patients. In addition, we sincerely hope that it will stimulate further research on RA susceptibility which will in turn allow more robust and specific dietary recommendations to be made.

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